U.S. Food and Drug Administration

Notice: Archived Document

The content in this document is provided on the FDA's website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.

HIV Efficacy Data Specification

Wen Zeng, Greg Soon

FDA/CDER/OB/DBIV

The views expressed in this talk are those of authors, not of the FDA

DIA, April, 2010

Outlines

- Purpose of This Specification
- Brief Introduction of HIV Trials
- Specification in Details
- Summary

Purpose of This Specification

- To facilitate the reviewing process
  - -- Standard datasets ("One Statistical Procedure Away")
  - -- Standard variable names (Reusable programs across sponsors)

- To prepare for future meta-analysis
  - -- To answer some critical future design questions (Non-inferior margin, endpoint evaluation, safety analysis, etc)

Brief Introduction of HIV Trial

48 weeks Treatment

Day 1 **Wk 48**

WK 0 2 4 8 16 24 32 40 48

Cocktail treatment

Study drug + OBT* *vs.* Placebo (or active control) + OBT

Repeated Measures

- HIV-1 RNA viral load
- CD4+/CD8+ count
- Lab: Chemical, hematology, Urology

* OBT: optimal background treatment.

Brief Introduction of HIV Trial - 02

48 weeks Treatment

Day 1 **Wk 48**

WK	0	2	4	8	16	24	32	40	48

Primary Efficacy Endpoint

- Percentage of subjects with <400 and/or <50 copies/mL of HIV-1 RNA viral load at Week 48 window (Snapshot)

Some Key Secondary Efficacy Endpoints

- Percentage of subjects with <400 and/or <50 copies/mL of HIV-1 RNA viral load through Week 48 window (**TLOVR** – time to loss-of-virologic response)
- Reduction of $\log_{10}$ HIV-1 RNA viral load from Baseline to week 48
- Change in CD4+ count from BL to week 48
- Sometimes, week 24 and week 96 were also be analyzed

Brief Introduction of HIV Trial - 03

Currently, there are close to 30 drugs approved for HIV treatment.

Drug Classes

- Nucleoside Reverse Transcriptase Inhibitors (NRTIs) – Retrovir …
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) – Sustiva …
- Protease Inhibitors (PIs) -- Kaletra …
- Fusion Inhibitors (FIs) -- Fuzeon
- Integrase Inhibitors (IIs) – Isentress …
- CCR5 Inhibitors (CCR5) – Selzentry

Special Notes

- The specification was developed prior to ADaM documents being finalized
- There are aspects in the specification that are not consistent with the current ADaM structures
- We try to follow ADaM as much as we can. If not, we will try to follow SDTM. If still no direct information, we will try to follow their conventions
- This specification is a living document and we hope to move towards consistency with ADaM as much as we can

Specification

For datasets additional to sponsor's regular data submission.

Datasets

One record per subject (our "ADSL")

- Subject characteristics and subject-level covariates
- Efficacy outcomes and related covariates

  (Efficacy part is not consistent with ADaM standard)

Multiple records per subject

- Raw HIV viral load data
- Immunology data (CD4+ count)
- Safety data (Lipids, Liver, Renal, Hema., etc)

(By visit and derived window)

ADSL: Analysis Data Subject Level

Specification -- 02

6 columns for each variable to be explained – like define. file

Variable Name (max=8)	Variable Label	Type	Codes (example)	Origin	Comments
1. Demog (DM)					
StudyID	Study Identifier	Char			Unique identifier for a study.
USUBJID	Unique Subject identifier	Char			Unique among all patients submitted for the product.
SUBJID	Subject ID for the study	Char			Subject identifier, which must be unique within the study. Often the ID of the subject as recorded on a CRF.
Sex	Sex	char			Sex of the subject.
SexCD	Sex code	Num	1=MALE, 2=FEMALE		Optional

ADaM specified columns

Variable Name	Variable Label	Type	Controlled Terminology	Definition

Specification in Details – 1/subject (our "ADSL")

Efficacy Outcomes and Related Covariates

1. Demographic variables
2. Baseline characteristics
3. Exposure variables (first and last dosing date, etc, ...)
4. Population flags (ITT, PP, etc,...)
5. Efficacy outcomes (primary, secondary, etc,...)
6. Covariates and subgroup variables
7. Subject disposition variables

Efficacy outcomes are the only component not in ADaM's ADSL.

Specification in Details – 1/subject

1. Demographic variables

StudyID	SubjID	USubjID	SiteID
BRTHDTC	Sex	Race	ETHNIC
ARM	ARMCD		
RFstdtC	RFendtC	RFstdt	RFendt

2. Baseline characteristics

(including Baseline Genotypic and Phenotypic Data, stratification factors, etc,...)

Region	VloadBLN	Str_CD4

T_PI: total # of PIs in OBT;

P_PI: phenotypic sensitivity score for PIs;

G_PI: genotypic sensitivity score for PIs;

Specification in Details – 1/subject

3. Exposure variables

TRTA: treatment actual received; TRTP: treatment planned;

EXDUR: duration of treatment;

Variables for study drug change, for OBT changes, etc;

Here ADaM "old" naming convention was used, but has changed in final ADaMIG.

TRTA ➔ to TRT1A, TRTP ➔ TRT1P

4. Population flags

ITTFL PPROTFL FASFL SAFFL

Here ADaM naming convention was used. STDM uses ITT, PPROT instead.

Specification in Details – 1/subject

5. Efficacy outcomes (primary, secondary, etc,...)

V: virologic 24/48/96: analysis week

50/400: cutoff value of HIV-1 RNA

S/T: analysis method (Snapshot or TLOVR)

V24_S50	V48_S50	V96_S50	V24_S400	V48_S400	V96_S400

V24_T50	V48_T50	V96_T50	V24_T400	V48_T400	V96_T400

Currently, variables are listed horizontally, not vertically displayed

If in a separate analysis dataset, it would be consistent with ADaM standard)

Specification in Details – 1/subject

5. Efficacy outcomes (primary, secondary, etc,...)

For this kind of visit-wise data, vertically display could be used

Param	ParamCD	AVisit	AVal	AValC	
Snapshot <50 copies/mL	S50	Week 24	1		
Snapshot <50 copies/mL	S50	Week 48	1		
Snapshot <50 copies/mL	S50	Week 96	1		
Snapshot <400 copies/mL	S400	Week 24	0		
Snapshot <400 copies/mL	S400	Week 48	0		
Snapshot <400 copies/mL	S400	Week 96	1		

The Reasons to choice the horizontal display in this particular case

- Easier to do correlation analysis
- Easier for medical reviewers to use as they used to

Specification in Details – 1/subject

6. Covariates and subgroup variables

DrugCat: study drug category: NRTI, NNRTI, PI, FI, CCR5, etc

EFV: is Efavirenz in the randomized background regimen?

HCVF: Hepatitis C antibody at screening?

…

7. Subject disposition variables

DSCAT: Category for Disposition Event

DSDT: Date/Time of Collection

DSSTDT: start Date/Time of disposition event

…

Specification in Details – multiple/subject

For raw HIV-1 RNA viral load, CD4+ count, liver function, etc,…

USubjID	VisitNum	VisitDY	Visit	AnaWeek	LBTest	LBstResn	LBactDT	LBactDY
	1 2 3 4 …	-7 1 14 21 …		Screeing Baseline Week 2 Week 4 … Week 24 … Week 48 … Week 96	HIV CD4			-6 1 13

Summary

- This is a special case for HIV trials

  – We could try to standardize variable names by disease-specific since this is too detailed for CDISC docs to specify

- ADaM and SDTM and their IGs are very helpful

  -- Data structures and variable naming conventions

- This is a living document, and it will be updated with feedbacks from sponsors

Acknowledges

Presenters would like to thank statistical reviewers in Anti-viral team at FDA/OB for their inputs.

Reference

- CDISC – SDTM V1.2 and SDTM IG V3.1.2
- CDISC – ADaM 2.1 and ADaMIG 1.0 Draft

SDTM -- **S**tudy **D**ata **T**abulation **M**odel

ADaM -- **A**nalysis **Da**taset **M**odel